Immunohistochemical Detection of Notch1 Protein in Ameloblastoma and Odontogenic Keratocyst: A Retrospective Cohort Study

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ABSTRACT

Odontogenic tumors (OGTs) are oral tumors that are derived from cells of odontogenic apparatus and their remnants. OGTs are subclassified into epithelial, mesenchymal and mixed in relation to their histogenesis. Although they are relatively uncommon, constituting nearly 1% of all oral tumors, they however represent an important aspect of oral and maxillofacial pathology. Malignant OGTs are exceedingly rare, the majority of OGTs are benign, and some show a pattern of local aggression and high recurrence rate such as ameloblastoma (AM)(El-Naggaret *et al.*, 2017).

On the other hand, odontogenic cysts are more commonly encountered. They can be classified into inflammatory and developmental cysts. Most developmental cysts have good prognosis following enucleation, but others bare a high recurrence rate following the same treatment modality, like odontogenic keratocysts (OKC)(Neville, Allen and Damm, 2016).

The NOTCH gene provides instructions formaking a protein called Notch, a member of the Notch family of receptors. Mammals have four Notch genes (NOTCH1-4)(Harper et al., 2003). Notch receptors are large transmembrane proteins that normally communicate signals upon binding to transmembrane ligands expressed on contiguous cells. Attachment of a ligand to the Notch receptor leads to two successive proteolytic cleavages that liberate the cytoplasmic portion of Notch (Notch-IC) from the membrane. Notch-IC enters the nucleus and binds to a certain transcription factor, converting it from a transcriptional repressor into a transcriptional activator. This leads to transcriptional activation of downstream target genes. Notch signals are important for normal development of many tissues throughout the body, both before birth and after(Wilson and Radtke, 2006). It can play a role in self-annihilation of the cell (apoptosis), cell division (proliferation) and maturation (differentiation).

A peculiar aspect of Notch is its apparently opposite functions in tumor development, because it can act as an oncogene or as a tumor suppressor. This depends on signal strength, timing, cell type, and context. Notch acts as an oncogene if its normal function is as a gatekeeper of stem cells or as a regulator of precursor cell fate. Its tumor suppressor activity is detected in tissues where Notch signaling initiates terminal differentiation events(Bolos, Grego-Bessa and de la Pompa, 2007).

A special interest is now directed to Notch1 protein because it was proposed that

deregulated expression of the cytoplasmic part of the Notch1 protein causes T-cell acute lymphoblastic leukaemia (T-ALL) in humans, however in the same time, it is proposed it causes suppression of skin carcinoma(Radtke and Raj, 2003).

Regarding the potential oncogenic character of Notch1, Notch receptors and ligands are widely expressed in the hematopoietic system, indicating the important functions for Notch signaling in hematopoiesis. The essential function of Notch1 in T cell fate specification is the most well characterized function of a Notch receptor in hematopoiesis. In the absence of Notch1, bone marrow progenitors enter the thymus and develop into B cells, indicating that Notch1 'instructs' an early lymphoid progenitor to adopt a T versus B cell fate, indicating its possible oncogenic role(Radtke et al., 2004). Several reports and experiments have then established the relationship between Notch1 and T-ALL. Translocation in NOTCH1 results in encoding of abnormal Notch1 protein in T-cell progenitors. It was then proven that active NOTCH1 was a potent and specific inducer of T-ALL(Aster, 2005).

Referring to the tumor suppressor role of Notch1 protein in skin carcinoma, mutations in the NOTCH1 gene have been found in about 15 percent of head and neck squamous cell carcinomas (HNSCC). NOTCH1 gene mutations associated with this condition are acquired during a person's lifetime and are found only in tumor cells; these changes are known as somatic mutations. Mutations in the NOTCH1 gene may reduce or eliminate production of functional Notch1 protein or lead to production of a protein that is unable to participate in cell signaling. Without the tumor suppressor function of the Notch1 protein, cells can grow and divide without control, leading to tumor formation.((US), 2015)

As for odontogenic neoplasms, Notch1 protein can be evident in many types of odontogenic tumors, but was noted to be widely expressed in cases of ameloblastoma. It can be detected in all subtypes of AM as indicated by the study employed by(Siare *et al.*, 2010), despite showing different staining intensities. Current studies have speculated that Notch1 protein may contribute to the invasive potential of AM as stated by(da Costa *et al.*, 2016). Other studies indicate additional roles for Notch1 protein in the pathogenesis of such a tumor. For odontogenic cysts, it was found that Notch1 protein can be expressed in entities such as radicular cysts, dentigerous cysts and odontogenic keratocysts(GONÇALVES *et al.*, 2012) with positive expression found in all the examined OKC cases. Another study(Miranda da Costa *et al.*, 2019) suggested the correlation between Notch1 protein and the invasiveness of OKC.

Owing to the limited number of studies that investigate the possible mechanism of involvement in Notch1 protein in growth, differentiation and local invasion of odontogenic tumors and cysts such as ameloblastoma and odontogenic keratocyst respectively, as well as the clinical significance and current prevalence of such lesions in Egypt, the present aim of this investigation is to employ a study using immunohistochemical detection of Notch1 protein in the fore-mentioned lesions for the objective of knowing if Notch1 protein plays a role in their pathogenesis, in order to help provide a clearer understanding of them and allow usage of that knowledge in future treatment modalities.

The research question of this study is, does the level of immunohistochemical expression of Notch1 protein in ameloblastoma and odontogenic keratocyst

exceed 90% of the cases? Where is immunohistochemical expression of Notch1 protein localized in these two lesions?